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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,819	08/03/2001	Roland Buelow	39691-0005A	8351

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,819	BUELOW ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-20,22-30,67 and 69-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20,22-30,67 and 69-71* is/are rejected.

7)☒ Claim(s) *72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/21/05 has been entered. As requested, applicant's after-final amendment and response, previously non-entered- see the advisory action mailed on 7/25/05 have also been entered. Claims 1-16, 21, 31-66, 68, and 73-76 are canceled. Claims 17-20, 22-30, 67, and 69-72 are currently pending and under examination in the instant application. An action on the merits follow. Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC § 102

The rejection of previously pending claims 13-26 and 67-71 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,569,825 (1996), hereafter referred to as Lonberg et al., is withdrawn over canceled claims 13-16, 21, and 68, and maintained over amended claims 17-20, 22-26, 67, and 69-71. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection as discussed in detail below.

The applicant argues that the claims as amended now recite that the non-human sequences come from a non-human animal that generates antibody diversity primarily through gene conversion and/or hypermutation and that the claimed vectors allow the production the production of humanized antibodies with V region amino acid sequences encoded by more than one V region gene segment as a result of gene conversion. The applicant argues that Lonberg does not recognize the significance of gene conversion in rabbits as opposed to gene rearrangement in mice and that Lonberg did not observe any gene conversion in humans or mice. In response, while Lonberg exemplified transgenic vectors useful for making mice and transgenic mice comprising human Ig sequences, Lonberg further teaches transgenic vectors useful for making transgenic rabbits (Lonberg et al., column 10, lines 46-60). Rabbits produce immunoglobulin diversity primarily using gene conversion, thus meeting the claim limitation. There is no requirement that Lonberg recognize or teach the applicant's particular motivation for using rabbits versus mice. In addition, contrary to applicant's arguments, Lonberg et al. does in fact teach the human Ig gene segments are flanked and separated by non-coding sequences derived from the non-human animal. As stated in the rejection of record, Lonberg teaches that non-coding switch regions flanking the human constant region gene or genes are derived from those that occur naturally in the germline of the species that is to receive the transgene construct, i.e. a rabbit, and further that additional regulatory sequences in the transgene are also derived from the non-human animal (Lonberg et al., column 8, lines 19-2 1, and column 9, lines 3-6). Finally, the claims as amended state that the humanized Ig locus is "capable of undergoing gene conversion ... in the non-human animal", thus producing a V region encoded by segments of more than one V region gene. The rejected claims are product claims to a transgenic vector, and

the claim language refers to the intended use of the vector for producing a transgenic non-human animal. Whether or not gene conversion occurs for any particular locus is a function of the species of mammal in which the locus resides, the developmental stage of the mammal, and the state of differentiation of the B cell containing the locus. The art at the time of filing does not teach the gene conversion requires any species specific gene sequences, all that is required is the presence of multiple V regions genes with regions of homology that allow gene conversion. Further, it is noted that gene conversion in antibody V regions can occur in mice- see for instance Tsai et al. (2002) Int. Immunol., Vol. 14 (1), 55-64. Therefore, by following the teachings of Lonberg to use the transgenic vector to make transgenic rabbits, the encoded immunoglobulin loci would be in an environment favoring gene conversion over rearrangement. As such, the transgene construct taught by Lonberg meets the claim requirement as being "capable" of undergoing gene conversion. Therefore, applicant's arguments are not found persuasive and the rejection of record is maintained.

The rejection of claim 76 under 35 U.S.C. 102(a) as being anticipated by Rader et al. (May, 2000) J. Biol. Chem., Vol. 275, No. 18, 13668-13676, is withdrawn in view of applicant's cancellation of claim 76.

Claim Rejections - 35 USC § 103

The rejection of claims 27-30 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,202,238 (1993), hereafter referred to as Fell et al., in view of Rader et al. (May, 2000) J. Biol. Chem., Vol. 275, No. 18, 13668-13676, is maintained. Applicant's amendments

and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection as discussed in detail below.

The applicant argues that the claims as amended now recite that the vector produced according to the claimed method contains non-human regulatory sequences and that the human gene segment is flanked by non-coding sequences from the non-human animal. As argued above concerning the teachings of Lonberg, the applicant states that neither Fell nor Rader recognized the significance of gene conversion in rabbits or demonstrate that a vector produced by the Fell methods could undergo gene conversion. Specifically, the applicant states that the vectors of Fell are inoperable because they would not produce humanized antibodies in rabbits through gene conversion. In response, the vector taught by Fell et al. contains the entire murine heavy chain including introns and murine regulatory sequences, wherein only the coding region of a murine variable region gene or constant region gene is replaced by a human variable or constant region gene (see in particular Fell et al., column 14, example 6, and Figure 1). Thus, the vectors taught by Fell et al. do in fact contain non-human regulatory sequences and the introduced human gene is in fact flanked by non-coding non-human sequences.

While it is true that the vectors of Fell et al. use murine sequences and that the mouse is not a mammal that primarily uses gene conversion to produce antibody diversity, the rejection of record is based on the combined teachings of Fell et al. in view of Rader et al. The rejection of record teaches that Rader et al. supplements Fell et al. by providing motivation for making chimeric rabbit antibodies over murine antibodies. Rader et al. teaches that,

> "compared with the other existing sources of human or humanized antibodies, immune rabbits are an attractive alternative for several reasons...epitopes that are not immunogenic in mice, a species from which the vast majority of monoclonal antibodies to human antigens has been generated, might be immunogenic in rabbits. This is of

> particular interest for the development of therapeutic human antibodies that are evaluated in mouse models and are required to recognize both the human antigen and its mouse homologue" (Rader et al., page 13674, column 2).

Rader et al. also teaches that the rabbit Ig gene repertoire is well characterized (Rader et al., page 13674, column 2). Therefore, in view of the specific advantages of producing humanized antibodies in rabbits over mice as taught by Rader et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to follow the methods of Fell et al. using rabbit immunoglobulin loci instead of mouse immunoglobulin loci. The rabbit loci naturally contains rabbit regulatory sequences and other non-coding sequences. Thus, following the teachings of Fell et al., the resulting vector would contain the entire rabbit heavy chain loci including regulatory regions wherein only the coding region of either a variable region gene or constant region gene has been replaced with a human variable region or constant region gene. As such, the combined teachings of Fell et al. in view of Rader et al. do in fact produce a vector in which the human sequence is flanked by rabbit non-coding sequence and which further contains rabbit regulatory sequences. Finally, since the rabbit loci does in fact undergo gene conversion in the rabbit, the resulting vector also meets the claim limitation of permitting gene conversion. Therefore, the rejection of record is maintained.

Claim Rejections - 35 USC § 112

The rejection of previously pending claims 67-72 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's cancellation

of claim 68 and amendment to claim 67. However, please note that the amendment to claim 67 fails to underline the word "flanked" which was amended. The applicant is notified that all future amendment must strictly comply with the requirements of 37 CFR 1.121(c) regarding claim amendments.

Claim Objections

Claim 72 is newly objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for

electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER